T790M negativo: E agora?

www.heldernovaisbastos.pt

Coimbra, 16 de Março de 2019

SÃO JOÃO HOSPITAL

FACULDADE DE MEDICINA DO PORTO 1825

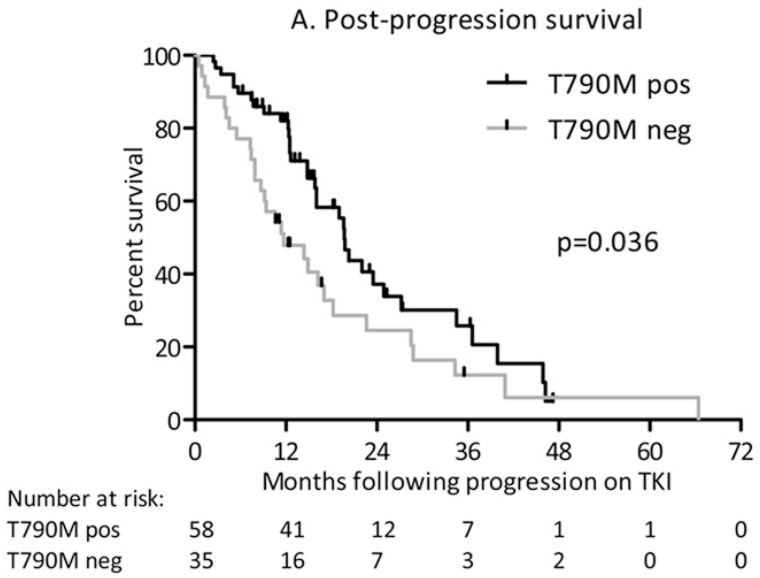
IBMC INSTITUTO DE BIOLOGIA MOLECULAR E CELULAR
INSTITUTE FOR MOLECULAR AND CELL BIOLOGY

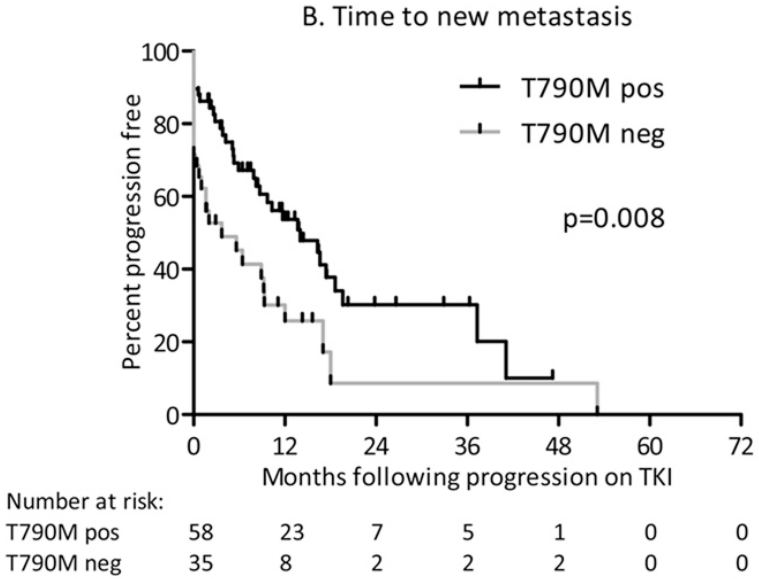
3S INSTITUTO DE INVESTIGAÇÃO E INOVAÇÃO EM SAÚDE
UNIVERSIDADE DO PORTO

Questões para discutirmos hoje

- Tumores *EGFR* T790M positivos e negativos são biologicamente diferentes?
- Quais os elementos de decisão clínica após progressão com EGFR-TKI de 1ª linha?
- Qual o papel da terapêutica-alvo (monoterapia ou combinada) nos tumores *EGFR* T790M negativos?
- A quimioterapia continua a ter um papel neste contexto?
- E a imunoterapia?....

Doença mais agressiva em tumores T790M neg



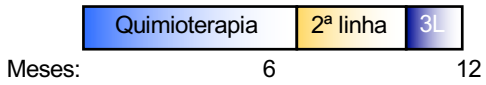


- Na era pré-Osimertinib, doentes T790M+ apresentavam PFS significativamente mais longa (P=0.036)
- Doentes T790M-negativos progridem mais frequentemente com metastização “de novo” e com maior deterioração clínica

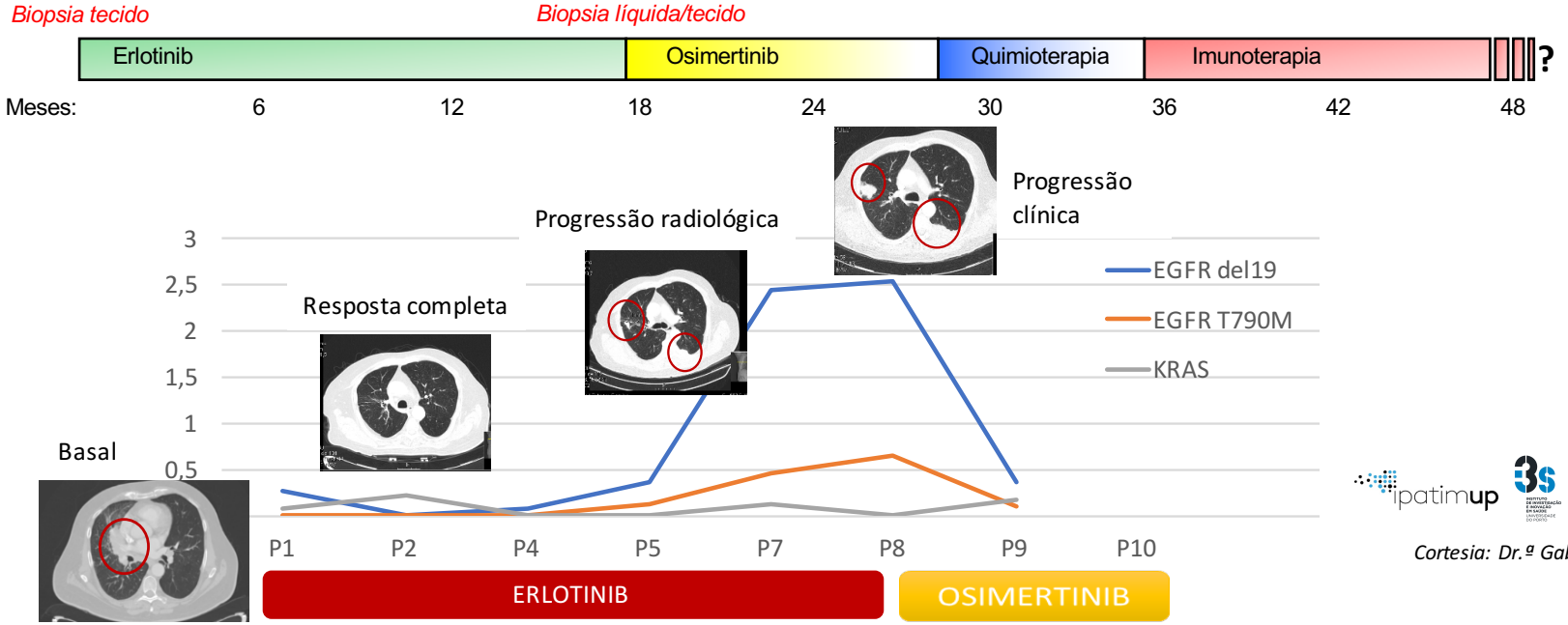
Oxnard et al. Clin Cancer Res. 2011

O caminho para a cronificação do cancro de pulmão

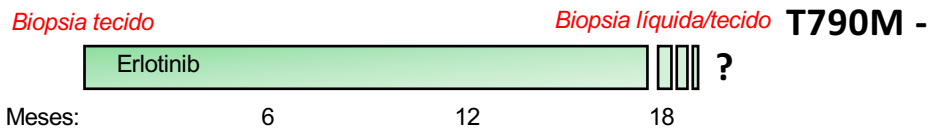
Tratamento de doente *EGFR*+ em 2008:



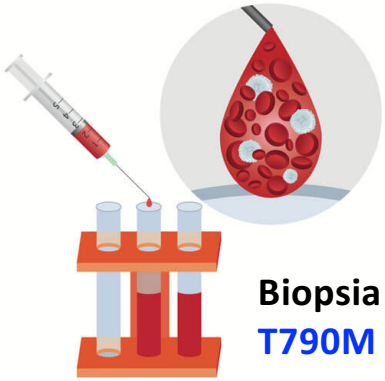
Tratamento de doente *EGFR*+ em 2019:



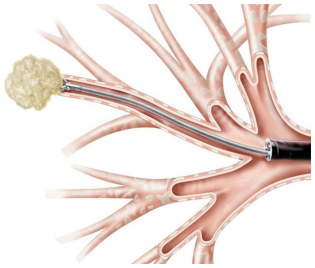
Cortesia: Dr.ª Gabriela Fernandes



CENÁRIO 1:



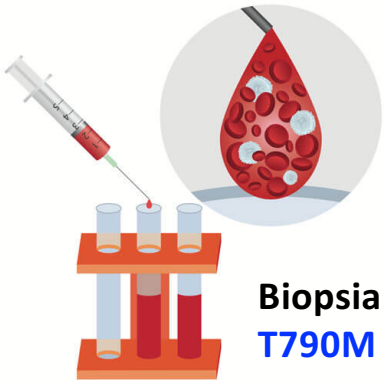
Biopsia líquida
T790M neg



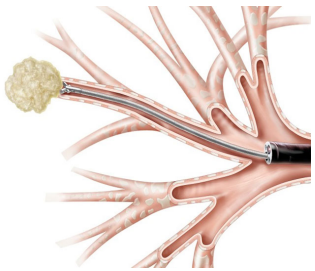
Biopsia de tecido
T790M pos

Osimertinib

CENÁRIO 2:



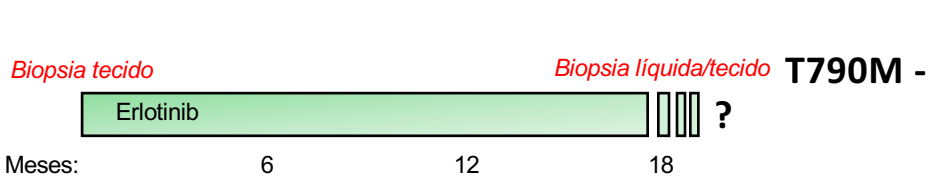
Biopsia líquida
T790M neg

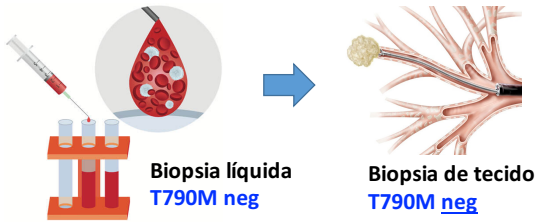


Biopsia de tecido
T790M neg

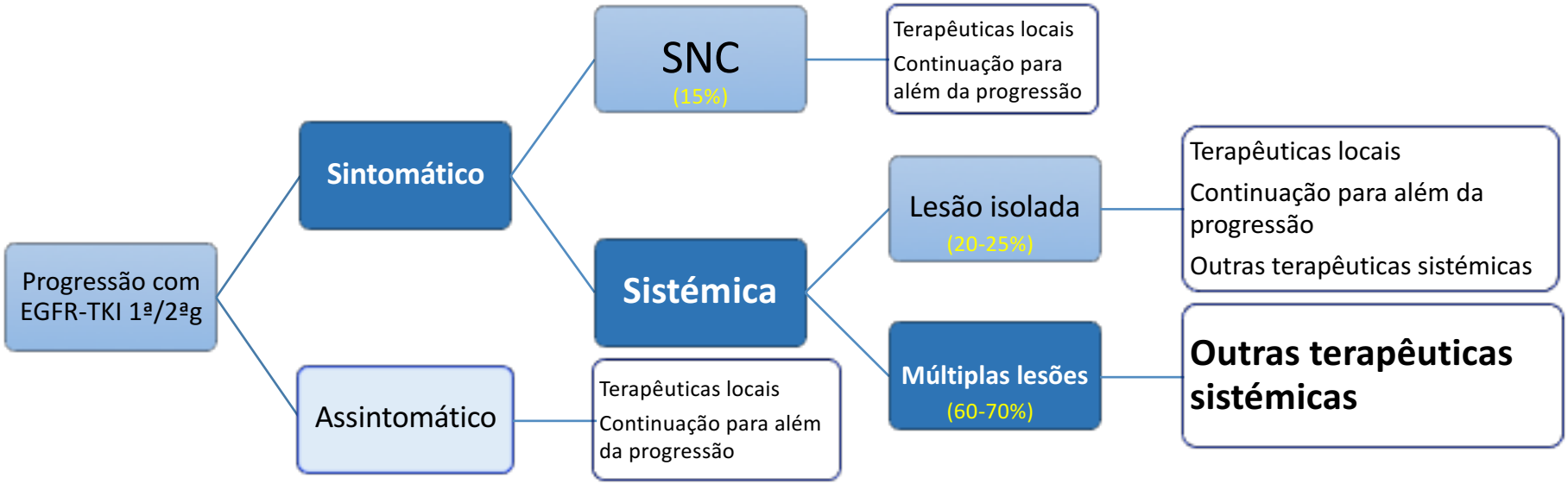
Várias opções:

- Sintomático?
- Oligoprogressão vs progressão sistémica?



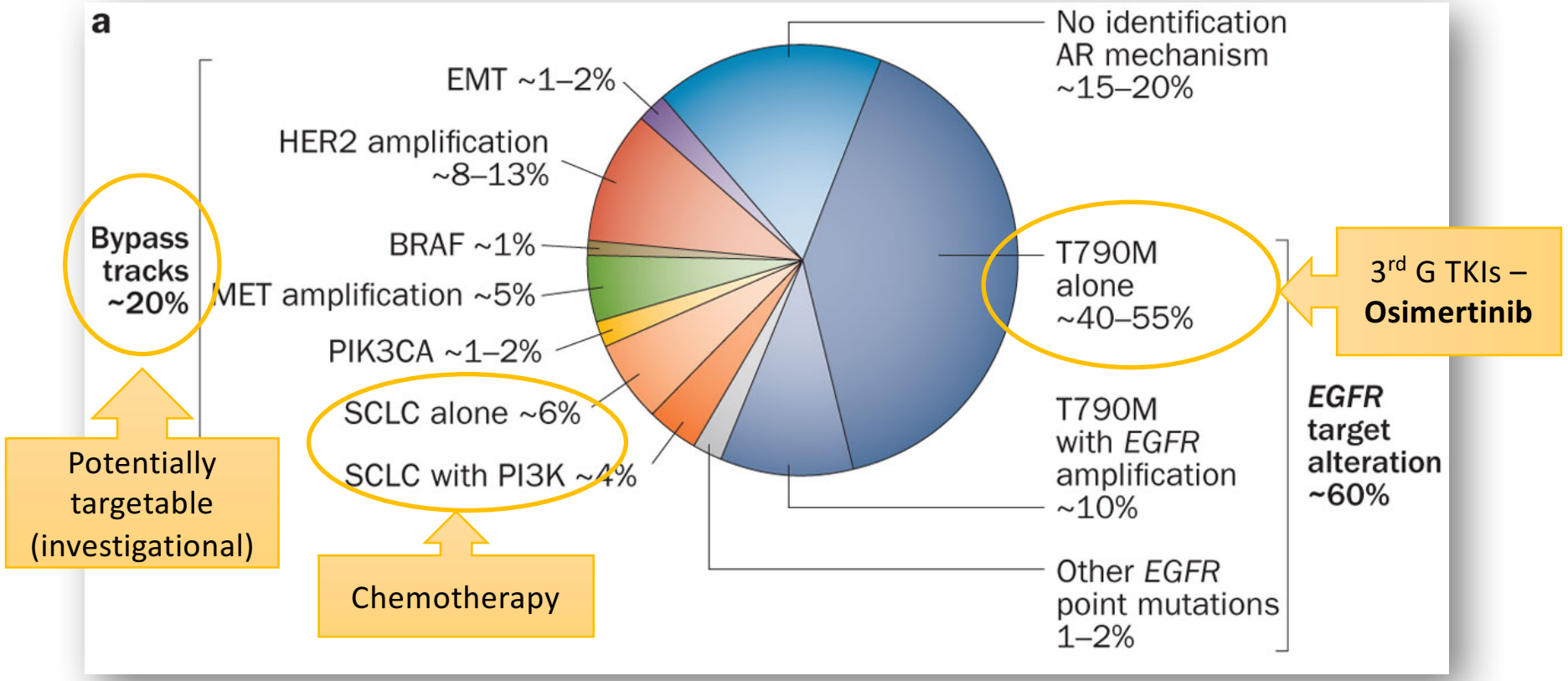


Várias opções:
- Sintomático?
- Oligoprogressão vs progressão sistémica?



NCCN National Comprehensive Cancer Network®

Mecanismos de resistência adquirida aos EGFR-TKI 1ª/2ª ger



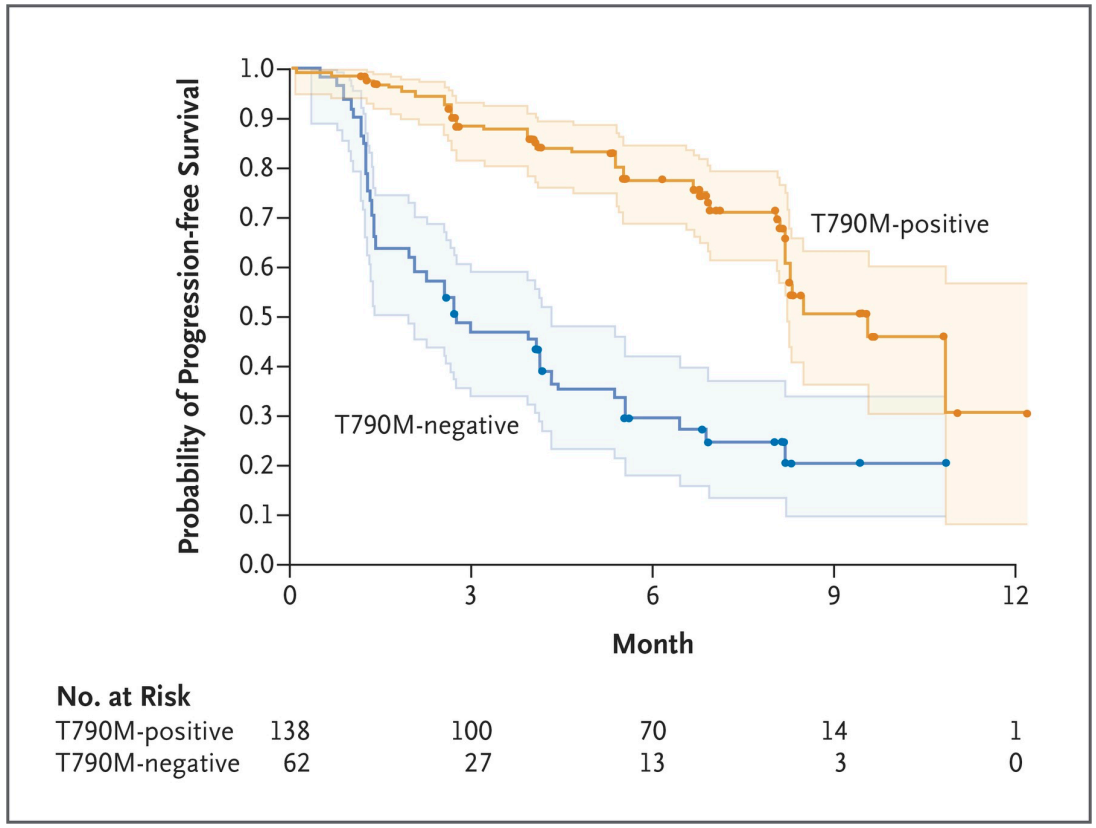
Camidge, *et al. Nat. Rev. Clin. Oncol.* 2014 doi:10.1038/nrclinonc.2014.104

Osimertinib (AURA 1)

- NSCLC metastático ou localmente avançado
- Progressão após EGFR-TKI

	T790M pos	T790M neg
OR	61%	21%
PFS	9.6 meses	2.8 meses

OR – overall response; PFS – progression free survival



Jänne et al. NEJM 2015

Rociletinib (TIGER trials)

- NSCLC avançado
- Progressão após EGFR-TKI
- **17/57 doentes T790M neg**

2015	T790M pos	T790M neg
OR	59%	29%
PFS	13.1 meses	5.6 meses

N Engl J Med. 2016 Jun 9;374(23):2296-7. doi: 10.1056/NEJMc1602688. Epub 2016 May 11.

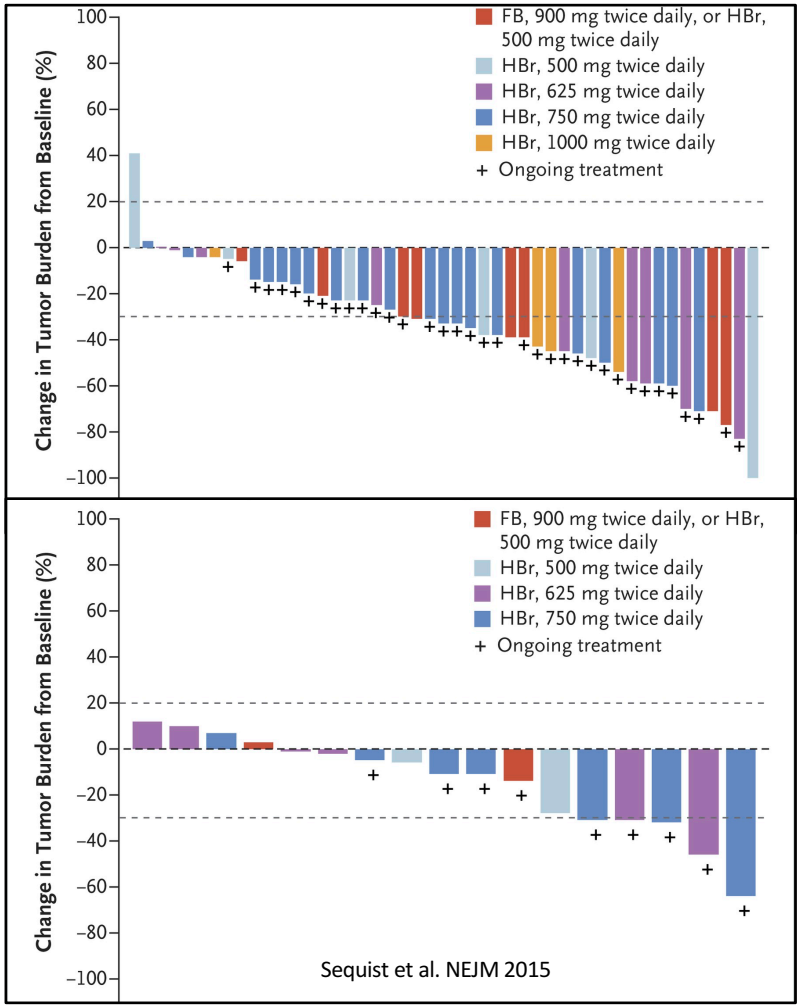
Update to Rociletinib Data with the RECIST Confirmed Response Rate.

Sequist LV[1], Soria JC[2], Camidge DR[3].

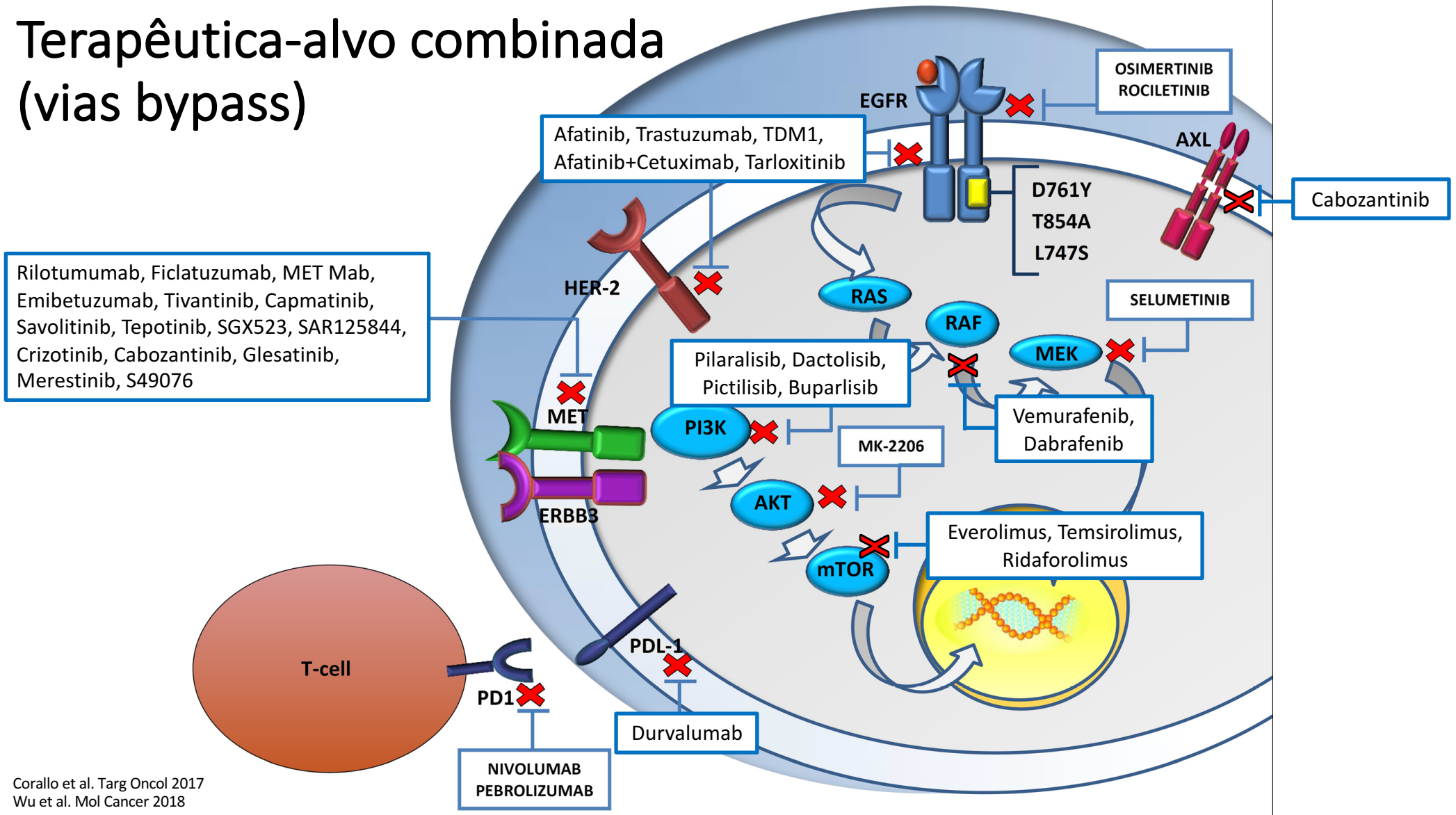
2016	T790M pos	T790M neg
OR	45%	17%

T790M-positivo

T790M-negativo

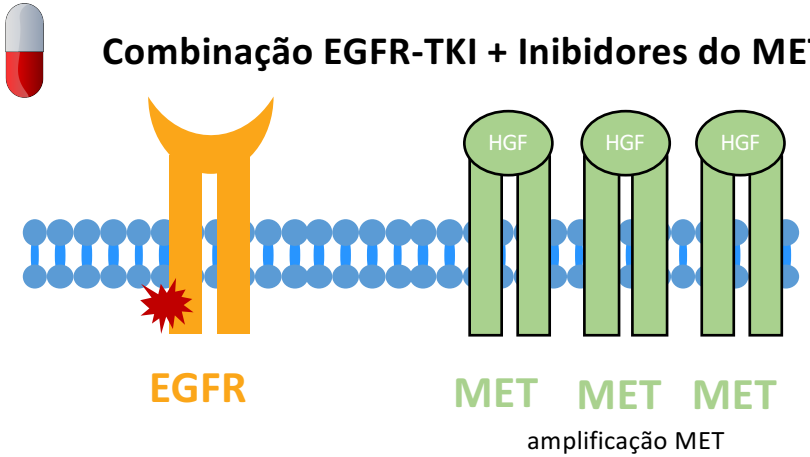


Terapêutica-alvo combinada (vias bypass)



Corallo et al. Targ Oncol 2017
Wu et al. Mol Cancer 2018

Combinação EGFR-TKI + Inibidores do MET



amplificação MET

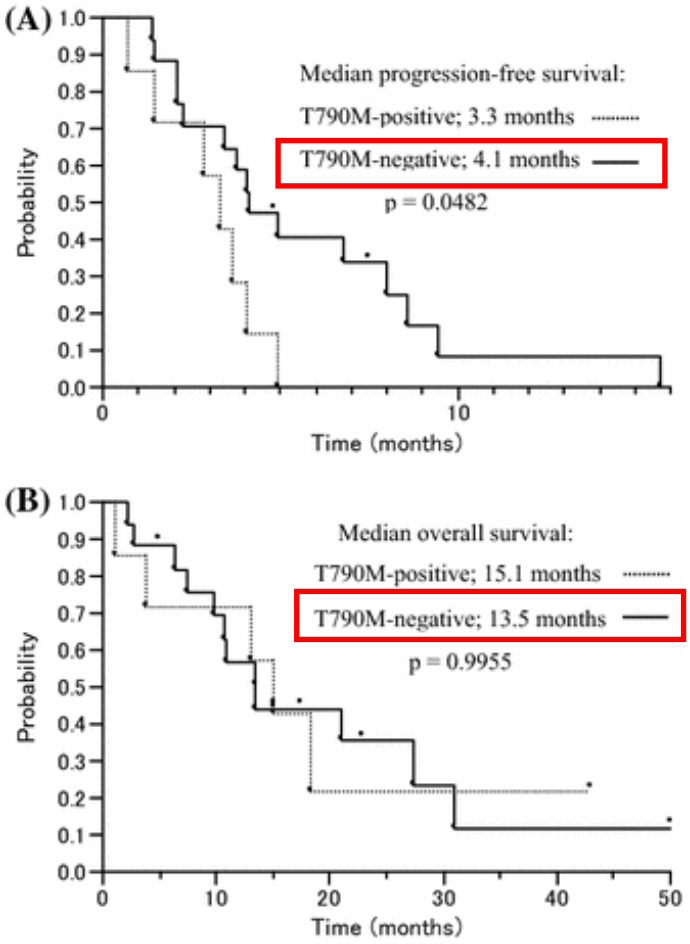
		n	ORR	PFS	
Amplificação do *MET*	Emibetuzumab ± Erlotinib	111	3%	3.3 m	Camidge et al. J Clin Oncol. 2016
	Tivantinib + Erlotinib	45	7%	2.7 m	Azuma et al. *ESMO Open. 2016*
	Capmatinib + Gefitinib	83	30%*	5.5 m*	Wu et al. J Clin Oncol. 2016
	Crizotinib + EGFR-TKI	14	50%**	12.6 m**	Wang et al. J Transl Med. 2019

**EGFR* T790M+ foram excluídos, expressão cMET elevada e *gene copy number* ≥6 era requisito
***EGFR* T790M+ foram excluídos, amplificação MET (MET/CEN7 ratio ≥1.8) comprovada

EGFR-TKI ”*rechallenge*” + bevacizumab

- N=24 doentes com NSCLC *EGFR*+ e progressão após erlotinib, gefinitib ou afatinib

Erlotinib + bevacizumab (n=22)
Gefitinib + bevacizumab (n=2)



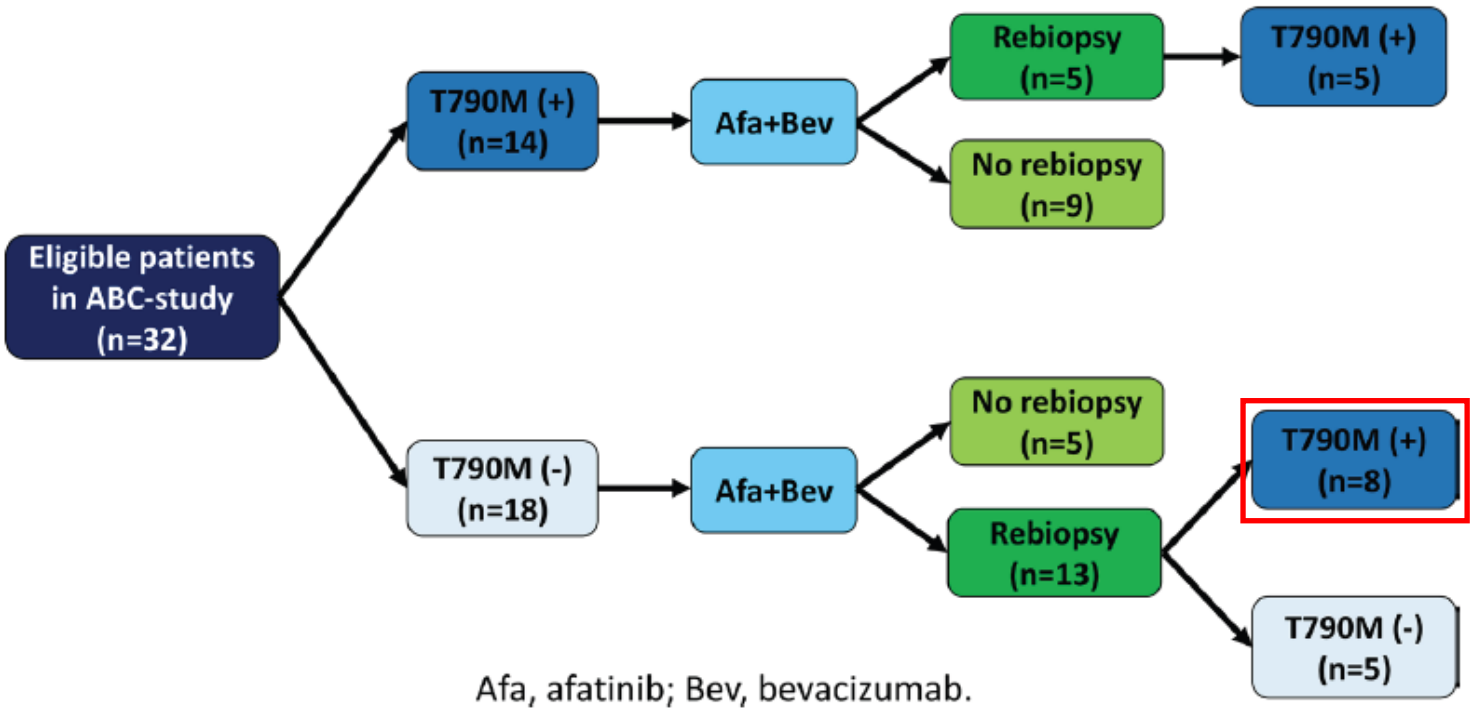
<u>Toxicidade grave (grau ≥ 3)</u>:
rash (4 %), paroníquia (4%), hipertensão (4 %), anemia (4 %)

Otsuka et al. Cancer Chemother Pharmacol. 2015

www.oncotarget.com Oncotarget, 2018, Vol. 9, (No. 78), pp: 34765-34771

Research Paper

Does afatinib plus bevacizumab combination therapy induce positive conversion of T790M in previously-negative patients?

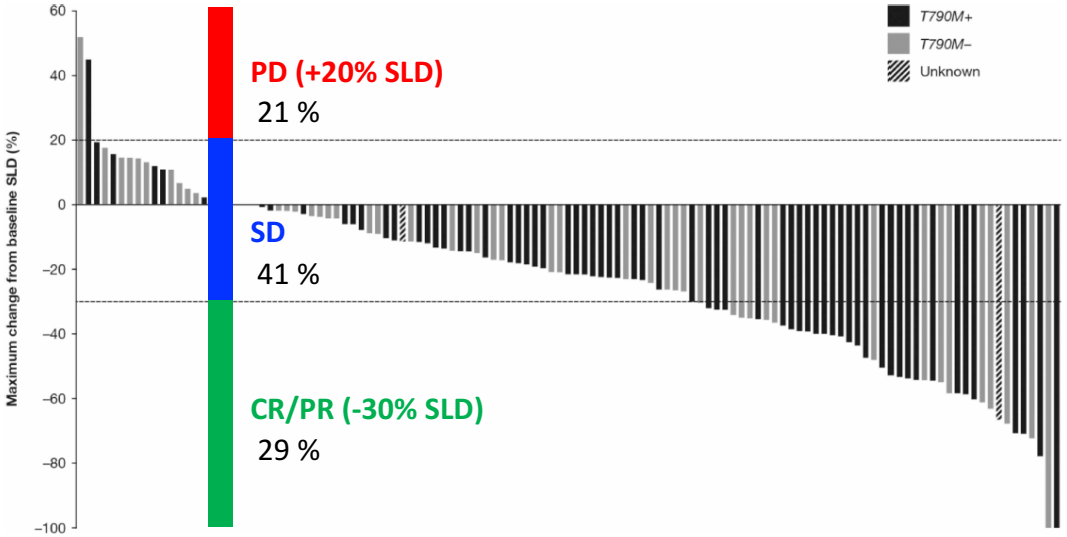


Afa, afatinib; Bev, bevacizumab.

Hata et al. Oncotarget 2018

Afatinib + Cetuximab

- N=126 doentes com progressão após erlotinib/gefinitib
- Ex19 del em 62%
- T790M+ em 57%



Toxicidade: rash (90%), diarreia (71%), paroníquia (57%), estomatite (56%), fadiga (47%), náuseas (42%)

EA grau 3 (44%): rash (20%), diarreia (6%)

EA grau 4 (2%): fadiga, pneumonite; Mortalidade associada ao tratamento em 2 doentes por dispneia e pneumonite

	T790M pos	T790M neg
OR	32%	25%
DoR	5.6 meses	9.5 meses
PFS	4.8 meses	4.6 meses

OR – overall response; DoR – duration of response; PFS – progression free survival

Janjigian et al. Cancer Discov 2014

Afatinib + Paclitaxel (LUX-LUNG 5)

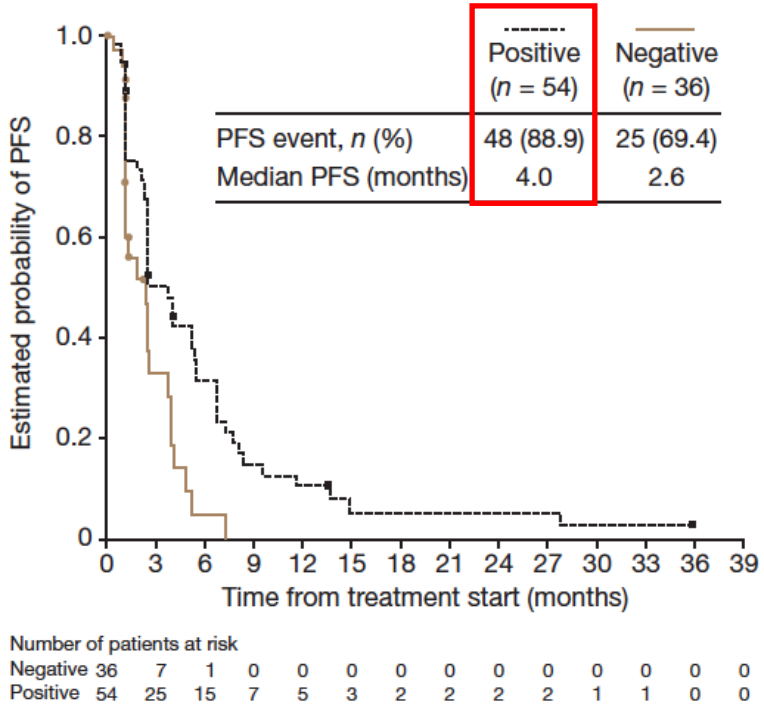
- NSCLC III-B/IV
- Progressão após ≥1 linha QT e após ≥12sem de erlotinib/gefitinib → ≥12sem afatinib (monoterapia) → PD

Toxicidade: diarreia (53.8%), alopécia (32.6%), astenia (27.3%), anorexia (22.0%), rash (20.5%) e Neuropatia periférica (9.1%)

Descontinuação por toxicidade em 19%

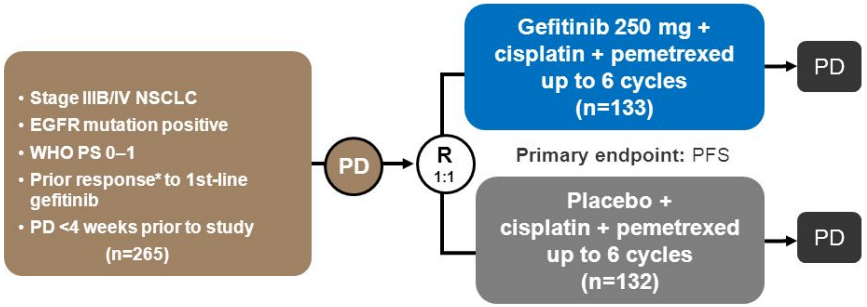
Mortalidade por pneumonia atribuída ao paclitaxel

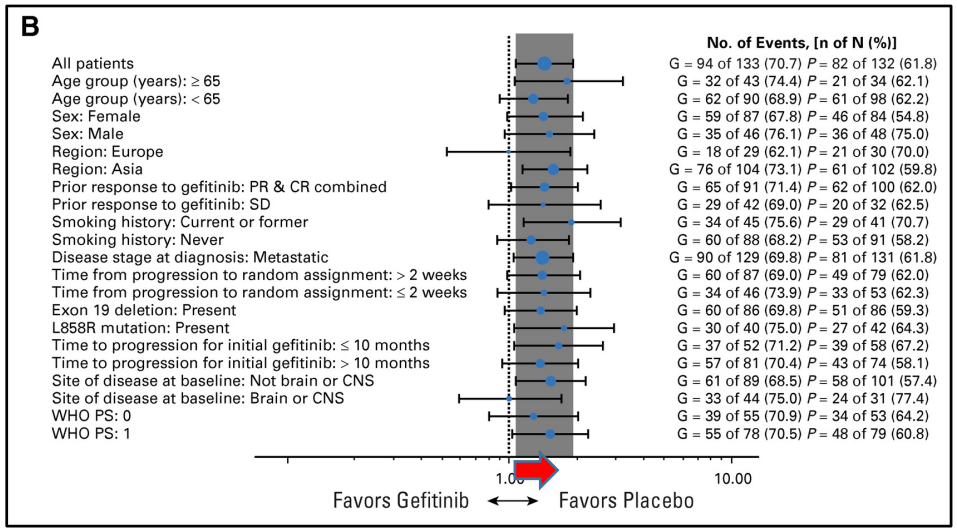
Subanálise de acordo com ***EGFR*** **mutation status**

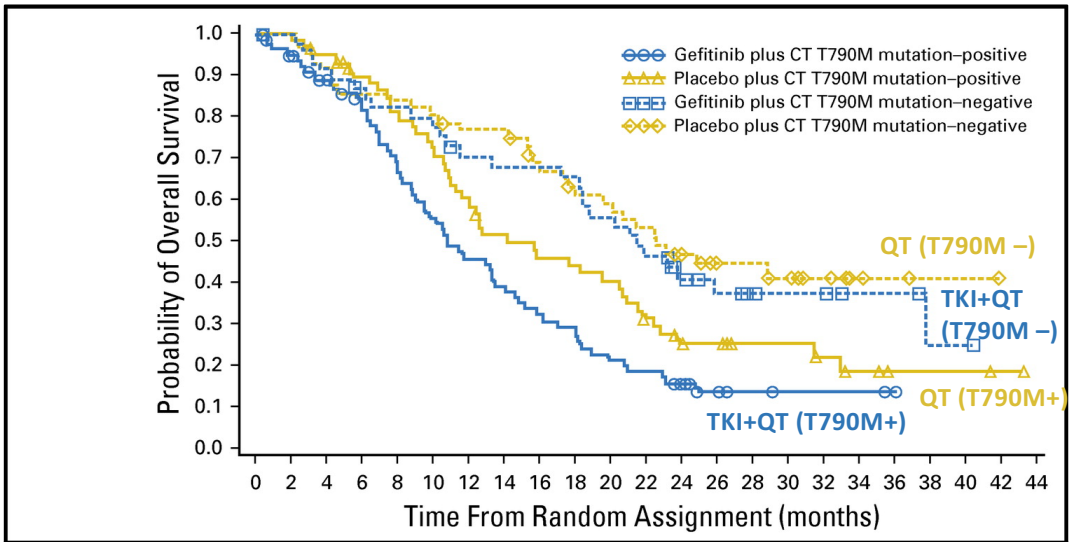


Schuler et al. Ann Oncol 2016

Cisplatina + Pemetrexed (IMPRESS trial)







T790M Mutation–Positive	Gefitinib Plus CT (n = 81)	Placebo Plus CT (n = 61)
Median OS, months	10.8	14.1
No. of events, No. (%)	63 (77.8)	44 (72.1)
HR (95% CI); *P* value	1.49 (1.02 to 2.21); *P* = .0432	

T790M Mutation–Negative	Gefitinib Plus CT (n = 46)	Placebo Plus CT (n = 59)
Median OS, months	21.4	22.5
No. of events, No. (%)	27 (58.7)	30 (50.8)
HR (95% CI); *P* value	1.15 (0.68 to 1.94); *P* = .6093	

Mok et al. J Clin Oncol 2017

Docetaxel + Nintedanib

- 62 doentes com NSCLC avançado refractário
- 28 doentes *EGFR*+, que progrediram após EGFR-TKI
  - 25/28 também progrediram pós-QT (dupleto com platino)

Toxicidade: neutropenia (53.2%), diarreia (37.1%)

Tratamento descontinuado em 19%

Oncology

Oncology 2019;96:51–58
DOI: 10.1159/000492472

Received: May 2, 2018
Accepted after revision: July 25, 2018
Published online: October 26, 2018

Impact of Epidermal Growth Factor Receptor Mutation on Clinical Outcomes of Nintedanib Plus Docetaxel in Patients with Previously Treated Non-Small Cell Lung Cancer from the Korean Named Patient Program

Sook-Hee Hong[a, g] Ho jung An[a] Kihyun Kim[b] Seung Sei Lee[c] Yun-Gyoo Lee[c]
Young-Jin Yuh[d] I Cheon Park[e] Yee Soo Chae[f] Tae-Won Jang[e] Jin-Hyoung Kang[a, g]

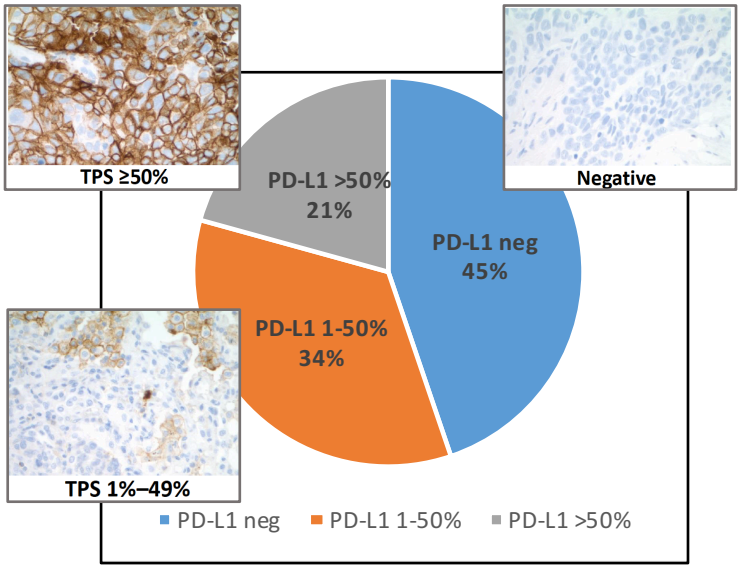
	EGFR positivo	*EGFR* negativo	P-value	LUME-Lung 1
ORR	39.3%	21.9%	P= 0.142	
PFS	6.5 m	3.3 m	P = 0.009	**3.4 m**

ORR - objective response rate; PFS – progression free survival

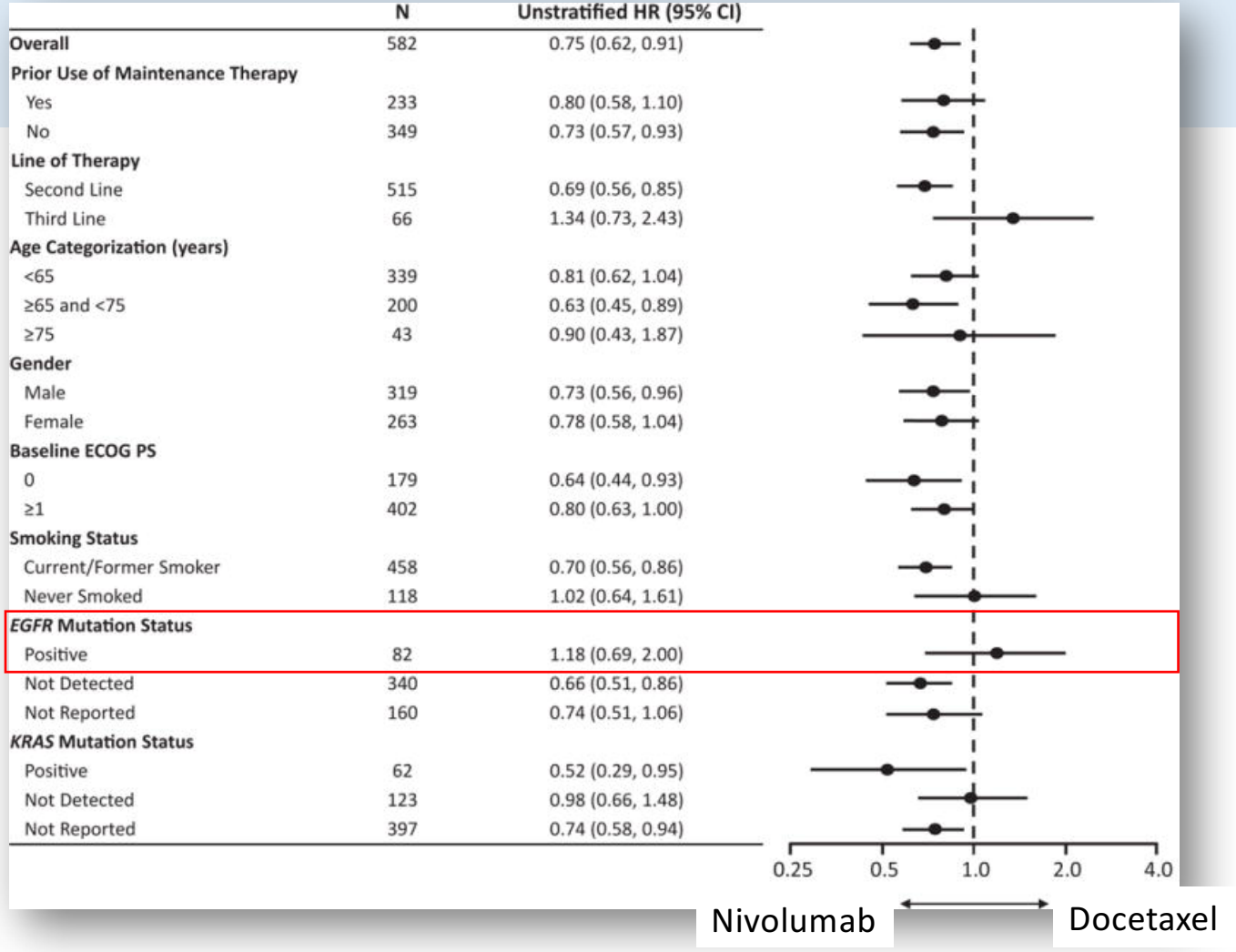
Hong et al. Oncology 2019 | Reck et al. Lancet Oncol 2014

Imunoterapia

Expressão PD-L1 em *EGFR* mutados no CHSJ



- Amostra de 165 doentes ADC III-IV
- *EGFR*+ em 18.2%
  - 55% são PD-L1+



Borghaei et al. NEJM 2015 | Herbst et al. Lancet 2016

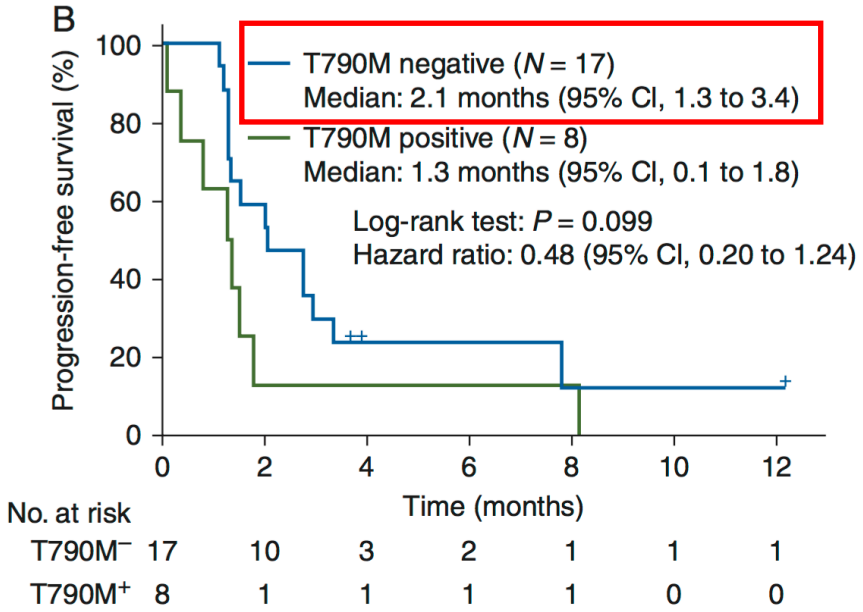
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28: 1532–1539, 2017
doi:10.1093/annonc/mdx183
Published online 12 April 2017

ORIGINAL ARTICLE

Tumor immune microenvironment and nivolumab efficacy in *EGFR* mutation-positive non-small-cell lung cancer based on T790M status after disease progression during EGFR-TKI treatment

NIVOLUMAB



	Cohort A		*P* value[a]
	T790M positive (*N*=8)	**T790M negative (*N*=17)**	
PD-L1 expression level	*N*=6	*N*=9	
≥1%	3/6 (50%)	5/9 (56%)	1.000
≥10%	1/6 (17%)	3/9 (33%)	0.600
≥50%	0/6 (0%)	2/9 (22%)	0.489
$CD8^+$TIL density (/mm^2)	*N*=4	*N*=10	0.572
Median (range)	365 (44–586)	381.5 (107–2292)	
$FOXP3^+$TIL density (/mm^2)	*N*=4	*N*=10	0.157
Median (range)	72 (39–91)	108.5 (57–373)	

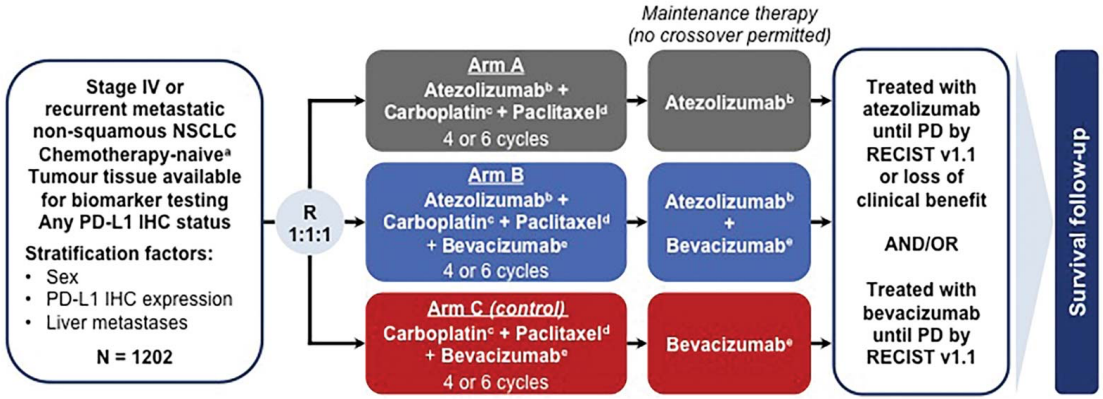
Haratani et al. Annals of Oncology 2017

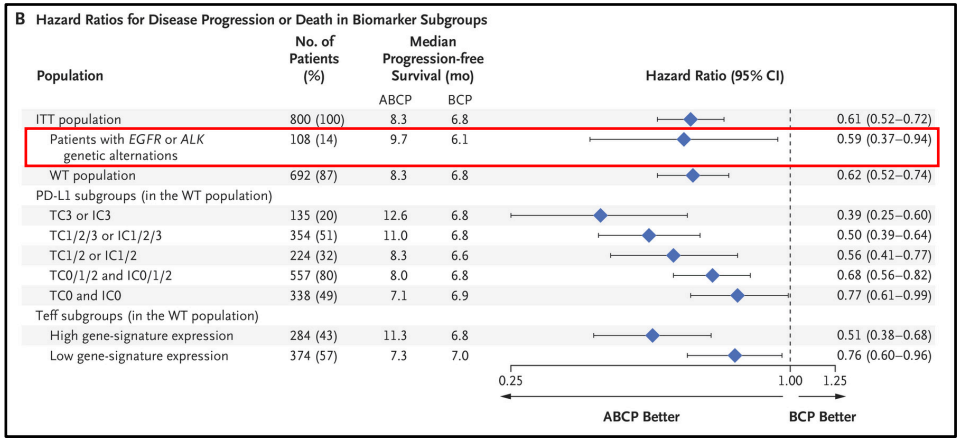
Combinação EGFR-TKI + Imunoterapia

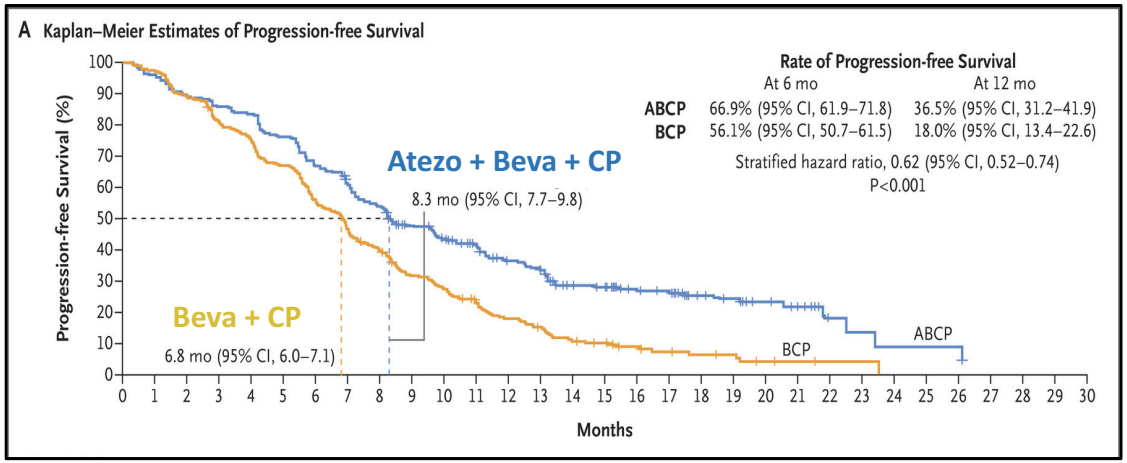
ClinicalTrials.gov identifier	Phase; population	Treatment	Status
NCT01998126	Phase I; EGFR TKI-naive or not	Nivolumab/ipilimumab + erlotinib	Ongoing, not recruiting
NCT01454102	Phase I; EGFR TKI-naive or not; CheckMate 012	Nivolumab + erlotinib (arm E)	Ongoing, not recruiting
NCT02574078	Phase I/II; EGFR TKI-naive or not (maintenance)	Nivolumab + erlotinib	Ongoing, not recruiting
NCT02039674	A Phase I/II; EGFR TKI-naive	Pembrolizumab + erlotinib (cohort E); pembrolizumab + gefitinib (cohort F)	Ongoing, not recruiting
NCT02364609	Phase I; erlotinib-resistant	Pembrolizumab + afatinib	Recruiting
NCT03157089	Phase II; squamous cell lung cancer; 3rd-line and more; (LUX-Lung IO)	Pembrolizumab + afatinib	Recruiting
NCT02013219	Phase I; EGFR TKI-naive	Atezolizumab + erlotinib	Ongoing, not recruiting
NCT02088112	Phase I; EGFR TKI-naive or not	Durvalumab + gefitinib	Ongoing, not recruiting
NCT01998126	Phase I; EGFR TKI-naive or not	Ipilimumab + erlotinib	Ongoing, not recruiting
NCT02040064	Phase I; EGFR TKI-pretreated; GEFTREM	Tremelimumab + gefitinib	Ongoing, not recruiting
NCT02906163	Phase I/II; EGFR TKI-naive	Afatinib, gefitinib, erlotinib + thymosin alpha 1 (a peptide immune modulator) (phase II) *vs.* afatinib, gefitinib, erlotinib	Ongoing, not recruiting

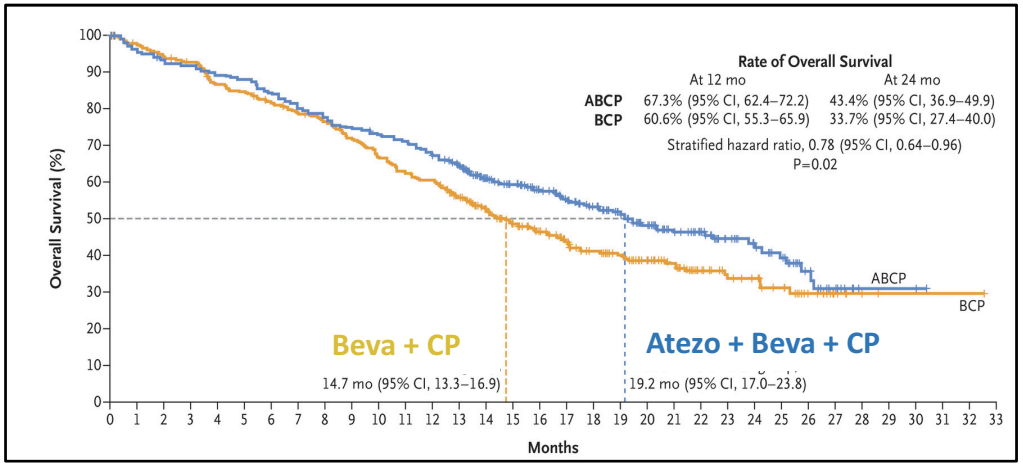
Karachaliou et al. Transl Cancer Res 2019

Atezo + Carbo + Paclitaxel + Beva (IMpower 150)





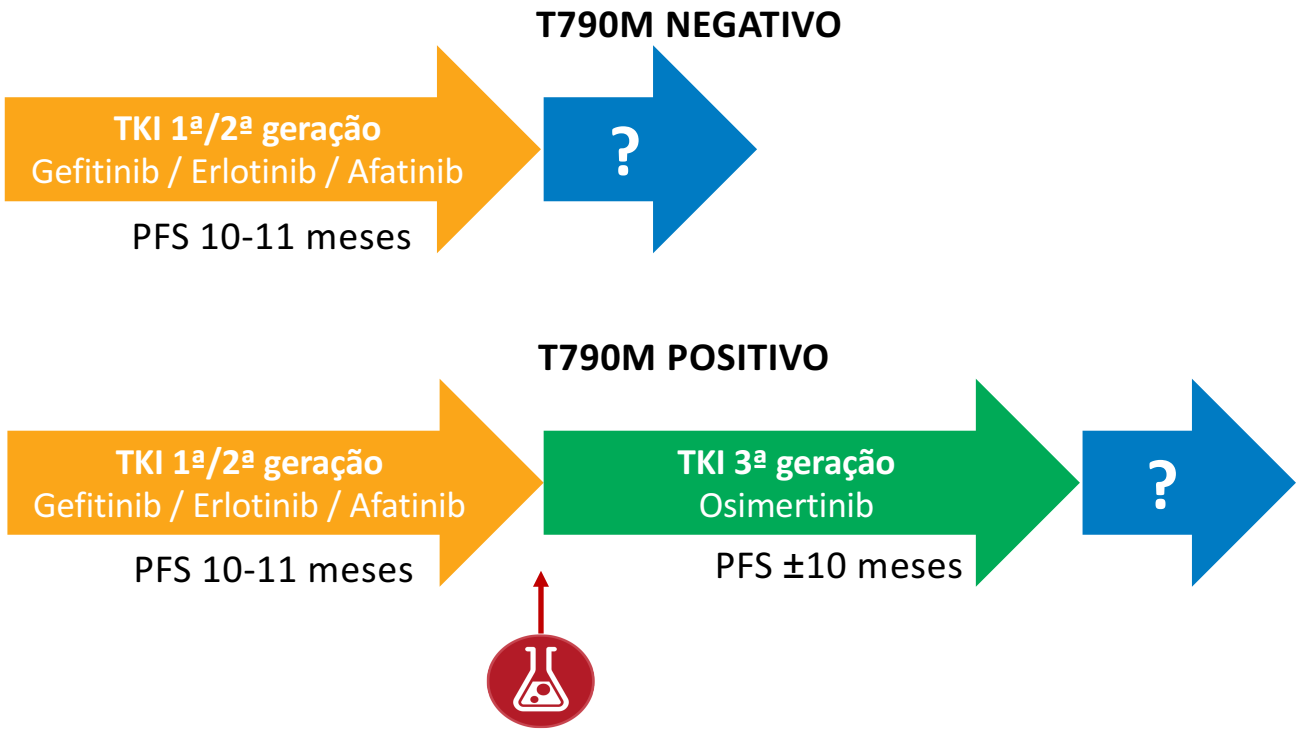




Socinski et al. NEJM 2018

	PFS	T790M status	Trial/Ref
Nivolumab	2.1	neg	Haratani et al. 2017
Osimertinib	2.8	neg	AURA1
Afatinib + Paclitaxel	4	neg/pos	LUX-LUNG 5
Erlo/Gefitinib + Beva	4.1	neg	Hata et al. 2015
Afatinib + Cetuximab	4.6	neg	NCT01090011
Cis + Pemetrexed	5.4	neg	IMPRESS
Docetaxel + Nintedanib	6.5	neg/pos	KCSG LU14-2
Atezo + Beva + CP	8.3	neg/pos	IMpower 150

Qual o melhor tratamento após progressão com *EGFR*-TKIs de 1ª/2ª geração?



Quimioterapia
± Antiangiogénico
± Imunoterapia